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Infra-low dose dipyridamole test

A novel dose regimen for selective assessment of myocardial viability by vasodilator stress echocardiography

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Low (0·56 mg . kg^{-1} over 4 min) and high (0·84 mg . kg^{-1} over 10 min) doses of dipyridamole can identify viable myocardium through the contractile recovery of basally dyssynergic regions; however, it also induces ischaemia in susceptible patients. The aim of this study was to assess the potential of an 'infra-low' dose of dipyridamole to selectively identify myocardial viability, independently evaluated by low dose dobutamine. Forty patients with resting dyssynergy and angiographically assessed coronary artery disease (1-vessel in 18, 2-vessel in 12, and 3-vessel in 10 patients) separately underwent a low dose dobutamine (5–10 μg . kg^{-1} . min^{-1} for 3 min) echo test and an infra-low dose (0·28 mg . kg^{-1} over 4 min) dipyridamole echo test. Systolic blood pressure (rest: 131 ± 19 mmHg) changed slightly after dobutamine (137 ± 21, $P<0·05$ vs rest) and remained stable after dipyridamole (130 ± 17, P=ns vs rest). Heart rate (rest: 68 ± 13 beats . min^{-1}) was also unchanged after dipyridamole (69 ± 12, P=ns vs rest) and increased slightly after dobutamine (71 ± 15, $P<0·05$ vs rest and vs dipyridamole). No patient developed echocardiographic or electrocardiographic signs of ischaemia after either dipyridamole or dobutamine. Of the 243 segments with baseline dyssynergy, 70 were responders (i.e. they showed an improvement of 1 grade or more, from 1=normal/hyperkinetic to 4=dyskinetic in a 16-segment model of the left ventricle) by both dipyridamole and dobutamine, 157 were non-responders (i.e. they showed no change) by both dipyridamole and dobutamine, and 16 showed discordant results (five responders by dipyridamole only; 11 by dobutamine only). The overall concordance of dipyridamole and dobutamine was 93%. An echocardiographic follow-up could be obtained >6 weeks after successful revascularization (achieved with angioplasty in 17, with by pass surgery in 3) in 19 patients and showed an improvement of one grade or more in 50 segments (viable) and no improvement in 50 segments (necrotic). The sensitivity of dobutamine and dipyridamole for predicting recovery was 76 and 78% respectively (P=ns); the specificity of both tests was 94%.

In conclusion, infra-low dose dipyridamole is a haemodynamically neutral stress test which does not affect either heart rate or systolic blood pressure; it allows myocardial viability to be explored selectively, without eliciting ischaemia; it shows excellent overall concordance with low dose dobutamine and has good sensitivity and excellent specificity for predicting functional recovery following successful revascularization.
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Key Words: Dipyridamole, dobutamine, viability.

Introduction

In a large subset of patients with chronic coronary artery disease and left ventricular dysfunction, left ventricular performance is reduced because the myocardium is regionally stunned or hibernating rather than irreversibly infarcted or fibrotic. The detection of reversible dysfunctional myocardium is clinically relevant, as regional or global left ventricular function will improve after revascularization[1,2]. To date, nuclear medicine, with positron emission tomography or thallium imaging, remains the accepted definitive method for clinical assessment of myocardial viability[3]. However, nuclear medicine is not always easily accessible and is expensive. Several alternative methods have been recently proposed for the clinical assessment of myocardial viability, such as pharmacological stress echocardiography, with either

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dobutamine[4–9] or dipyridamole[10,11]. With pharmacological stress, the principle (i.e. the underlying physiological marker) of the test relies on the demonstration of residual contractile reserve in a basally dysfunctional region: improved myocardial thickening of segments that are dyssynergic in resting conditions is a sign of viability, whereas necrotic segments show no functional improvement. Such reserve can be elicited either by direct stimulation of $\beta 1$ adrenoreceptors with low doses of dobutamine or through a flow-mediated increase in contractile function linked to endogenous adenosine accumulation achieved by intravenous infusion of dipyridamole[12]. An advantage of dobutamine over dipyridamole for viability assessment is the possibility of offsetting the inotropic dose for viability (up to 10 μg) from the higher ischaemic dose (up to 40 μg)[12]. The usefulness of dipyridamole stress as a stimulus for viability would increase if a dose regimen could be identified, capable of selectively exploring viability without eliciting ischaemia — similar to the way in which dobutamine works. Experimental data suggest that even very low doses of dipyridamole can improve function in stunned myocardium[13]. The aims of this study were: (1) to compare the accuracy of infra-low (0·28 mg . kg^{-1} over 4 min) dose dipyridamole, in identifying myocardial viability, with that of low (up to 10 μg) dose dobutamine — the most widely used of the pharmacological stress echocardiographic stimuli for viability recognition; and (2) to assess the systemic, haemodynamic and left ventricular function correlates of an infra-low dose of dipyridamole, substantially lower than the high dose regimen (0·84 mg . kg^{-1} over 10–min) usually employed for echocardiographic imaging, and also lower than the regular or low dose regimen (0·56 mg . kg^{-1} over 4 min) usually employed for perfusion imaging[14]. Therefore both tests were performed in 40 patients with coronary artery disease; of these 40 patients, 22 underwent a revascularization procedure, and echocardiographic follow-up after successful revascularization could be obtained in 19 patients.

Methods

Study population

Forty patients (33 men and seven women, age range 35 to 74 years, mean ± SD = 58 ± 10) with history of myocardial infarction, angiographically proven coronary artery disease, technically satisfactory acoustic windows and resting wall motion dyssynergy of the left ventricle were enrolled in the study. Thirty-eight patients had evidence of previous (>3 month) myocardial infarction, whereas two were examined early (within 3 weeks) after an acute myocardial infarction; 32 patients had a Q wave, and eight a non-Q wave infarction on the resting electrocardiogram. The site of myocardial infarction was anterior in 19 and inferior in 21 cases. Medical therapy was discontinued at least 48 h before the stress–echocardiographic examination in 26 subjects, while 14 patients received antianginal therapy: nitrates in two cases and combined therapy in 12 cases (nitrates and calcium antagonists in seven, calcium antagonists and beta blockers in five). Coronary angiography demonstrated significant stenosis (≥ 50% diameter reduction by quantitative coronary angiography) of one vessel in 18, two vessels in 12 and three vessels in 10 patients. The average left ventricular ejection fraction calculated from the apical 4-chamber view by 2-D echocardiography (single plane area-length method) was 41 ± 14%. Follow-up echocardiograms were obtained in baseline conditions in 19 patients at least 6 (9 ± 1) weeks after successful coronary revascularization.

Baseline echocardiographic examination

Two-dimensional echocardiograms were obtained using commercially available imaging systems (Hewlett-Packard 77020, 77025 or Diasonics, 2·5 and 3·5 MHz transducers). Echocardiographic images were recorded on VHS videotape for subsequent playback and analysis. Regional wall motion was assessed according to the recommendations of the American Society of Echocardiography with a 16-segment model[15]. In all studies, segmental wall motion was semiquantitatively graded as follows: Normal = 1; hypokinetic, marked reduction in endocardial motion and thickening = 2; akinetic, virtual absence of inward motion and thickening = 3; and dyskinetic, paradoxic wall motion away from the centre of the left ventricle in systole = 4. Baseline echocardiography was obtained before coronary angioplasty or coronary artery bypass surgery. Inadequately visualized segments were not scored.

Pharmacological stress echocardiography

All patients underwent, on separate sessions, and before coronary revascularization, low dose dobutamine infusion (5 μg . kg^{-1} . min^{-1} followed by 10 μg . kg^{-1} . min^{-1}, each step lasting 3 min) and an infra-low dose dipyridamole (0·28 mg . kg^{-1} over 4 min) echocardiography. Two-dimensional echocardiograms were continuously obtained and intermittently recorded during drug administration. In the baseline studies as well as during stress, all standard echocardiographic views were obtained when possible. During the procedure, the blood pressure and the electrocardiogram were recorded each minute. The videotapes were analysed by two independent cardiologist–echocardiographers, who were blind to the clinical and angiographic data. Digital acquisition of images of interest were obtained with a side-by-side display of rest and peak stress images in a cine-loop mode. A wall motion score index was derived for rest and peak stress (0 to 1 min after the end of each infusion) echocardiograms in all patients, as previously described for the baseline echocardiographic examination. A segment was considered to show signs of viability when it improved

by 1 grade or more at peak stress (for instance, a hypokinetic segment becoming normal, or an akinetic segment becoming hypokinetic). The level of inter-observer and intra-observer reproducibility of stress echo readings was >90% between the two echo laboratories participating in the study, as previously reported[16].

Echocardiographic follow-up

Coronary revascularization was performed in 22 patients: either by coronary artery bypass surgery (n=4) or by percutaneous transluminal coronary angioplasty (n=18). One patient died immediately after the procedure of acute heart failure, one patient had acute heart failure and ventricular fibrillation after the surgical intervention and needed a reoperation and in one patient early restenosis (within one month) occurred. In 19 patients a baseline follow-up echocardiogram was obtained at least 6 (9 ± 1) weeks after revascularization. None of these patients showed clinical, enzymatic, electrocardiographic or echocardiographic evidence of perioperative myocardial infarction, and all were thought to have had successful revascularization. Postoperative resting wall motion scores were determined as previously described by an experienced echocardiographer who was blind to stress echo results. Digital acquisition of images was obtained with a side-by-side display of baseline (pre-revascularization) and follow-up (post-revascularization) echocardiograms. Improved segmental wall motion at follow-up was defined as either endocardial excursion and wall thickening (score 1 or 2) in areas of akinesis or dyskinesis (score 3 or 4) at baseline, or normalization (score 1) of reduced endocardial excursion and wall thickening (score 2) at baseline.

Statistical analysis

Values are expressed as mean ± standard deviation. Differences in haemodynamic values before and after the infusions and in the wall motion score index under different conditions were tested for significance by analysis of variance and subgroup analysis by the Scheffé F test. Calculations of sensitivity, specificity and accuracy were performed according to standard definitions[17]. A P value <0·05 was considered statistically significant.

Results

Baseline echo findings

By inclusion criteria, all patients had regional dyssynergy in the resting echocardiogram. There were 243 segments with baseline dyssynergy: dyskinesis in 10, akinesis in 137, and marked hypokinesis in 96 segments.

Clinical and haemodynamic findings during pharmacological stress

None of the 40 patients had significant side effects or developed echocardiographic or electrocardiographic signs of ischaemia after either dipyridamole or dobutamine. In comparison with baseline, systolic blood pressure (rest=131 ± 19 mmHg) increased slightly after dobutamine (137 ± 21 mmHg, P<0·05 vs rest), whereas it did not change significantly after dipyridamole (130 ± 17 mmHg; P=ns vs rest; P<0·05 vs dobutamine). Heart rate (rest=68 ± 13 beats . min^{-1}) was also unchanged after dipyridamole (69 ± 12; P=nsvs rest), while a very mild increase was observed after dobutamine (71 ± 15, P<0·05 vs rest and vs dipyridamole).

Echocardiographic findings

Wall motion score index was 1·64 ± 0·32 at rest and improved significantly after dobutamine (1·51 ± 0·38 P<0·05 vs rest) and after dipyridamole (1·52 ± 0·39 P<0·05 vs rest, P=ns vs dobutamine). Of the 243 segments with baseline dyssynergy, 70 were responders (i.e. improved by one grade or more) with both dipyridamole and dobutamine, 157 were non-responders with both dipyridamole and dobutamine; and 16 showed discordant results (five responders by dipyridamole only, and 11 responders by dobutamine only). The overall concordance of dipyridamole and dobutamine in the 243 dyssynergic segments at baseline was 93%.

Follow-up resting echo

Follow-up echocardiography was available in 19 patients after successful coronary revascularization. Assuming as a viability criterion improved systolic wall thickening after dipyridamole in at least two adjacent abnormal segments, contractile reserve following dipyridamole was present in 11 (58%) of the 19 patients undergoing revascularization. Ten of the 11 patients with contractile reserve had improved systolic wall thickening after revascularization, whereas three of the eight patients without contractile reserve improved (91% vs 38%, P<0·05). At baseline echo at study entry, these 19 patients showed a total of 100 dyssynergic segments. Regional wall motion improved in time by one grade or more in 50 segments (viable) while in the remaining 50 (necrotic) no improvement could be observed. Of the 50 viable segments, dobutamine and dipyridamole correctly identified 37 and 38, respectively. Of the 50 necrotic segments, dobutamine and dipyridamole correctly identified 47 and 47, respectively (Fig. 1). The sensitivity of dobutamine and dipyridamole was 76% and 78% (P=ns), respectively. The specificity of both tests was 94%. Of the 40 segments identified as viable by dobutamine, 37 were also viable by dipyridamole; of the 60 segments necrotic by dobutamine, 56 were also necrotic

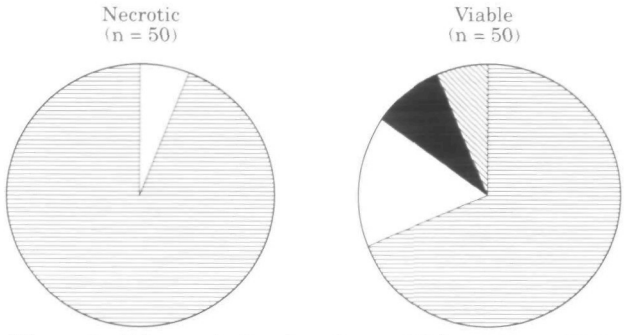

Figure 1 **Pie graph showing the sensitivity and specificity of dipyridamole (DIP) and dobutamine (DOB) in predicting functional recovery following revascularization. The two tests have comparable excellent specificity and good sensitivity. The numbers in parenthesis indicate segments. ■=identified by DOB and DIP; ■=identified by DOB only; ■=identified by DIP only; □=missed by DOB and DIP.**

by dipyridamole. The overall concordance of dipyridamole and dobutamine in the 100 dyssynergic segments at baseline was 93%

Discussion

Our results are in agreement with previous experimental and clinical studies demonstrating that ventricular dysfunction of viable tissue — due to either myocardial hibernation or stunning — can be improved by an inotropic stimulus with an accuracy of about 80% in predicting either spontaneous or revascularization-induced functional recovery[7–14]. Our study also showed that dobutamine and dipyridamole were similarly accurate in predicting recovery. This is consistent with preliminary reports showing comparable accuracy by high dose dipyridamole and low dose dobutamine in assessing myocardial viability[11,18]. In addition, the present study demonstrates for the first time, the feasibility, tolerability and accuracy of a very low dose dipyridamole regimen, especially designed as a coronary vasodilatory stimulus to selectively explore myocardial viability. This finding has potential clinical and pathophysiological relevance. From the clinical viewpoint, a low dose vasodilatory stress echo might be a suitable alternative to dobutamine stress echo for the selective assessment of myocardial viability, especially in patients with a history of malignant arrhythmias, or in those showing limiting side effects with low dose dobutamine[19].

From the pathophysiological viewpoint, the present data provide indirect support, in a clinical setting, for the concept that flow and function remain 'matched' in the hibernating heart[20,21], and that contractile reserve can be elicited in an equally effective way with a mild inotropic stimulus, increasing flow secondarily (as with dobutamine), or with a mild vasodilatory stimulus, increasing function secondarily (as with low dose dipyridamole).

The mechanism of viability recognition by infra-low dose dipyridamole

In this study myocardial viability was achieved with very low doses of dipyridamole, and with an accuracy similar to that reported with high dose dipyridamole[10]. In a dog model of stunned myocardium, Jeremy *et al.* showed that a significant improvement in % systolic thickening in the stunned area was achieved with very low adenosine doses, and the same improvement was obtained with adenosine doses up to 100 times higher[22]. This might explain why inotropic reserve can be recruited with similar efficacy by infra-low and high doses of dipyridamole. This differs from the ischaemic effect, which rises sharply with increasing doses[14].

Infra-low dose dipyridamole recruits inotropic reserve through two possible mechanisms: haemodynamic (linked to increased coronary flow) or metabolic (due to accumulation of endogenous adenosine).

Dipyridamole may increase post-ischaemic function by increasing flow through the Gregg phenomenon[23]: changes in vascular distension affect sarcomere length and thereby influence contractile function. This interpretation is consistent with experimental[24–27] and clinical[28] studies, demonstrating that residual flow reserve can be elicited in the presence of a severe coronary stenosis and depressed baseline function. In addition, myocardial contrast echocardiography[29] and positron emission tomography[30] studies have recently shown that the presence of residual coronary reserve following dipyridamole infusion identifies segmental viability in patients with wall motion abnormalities.

The second, and probably more likely, mechanism does not need the increase in coronary flow to improve function. In an experimental study on the dog model of stunned myocardium, Zughaib *et al.* showed that the augmentation of endogenous adenosine attenuates myocardial stunning independent of coronary flow or haemodynamic effects[31]. This conclusion is corroborated by the study of Ely *et al.*, who reported beneficial effects of adenosine on ischaemia–reperfusion injury in isolated hearts at constant coronary flow[32]. Several flow-independent beneficial effects of endogenous adenosine have been hypothesised including: blocking of slow calcium channels (with reduction of cytosolic accumulation of calcium); glycolysis stimulation; inhibition of free radical generation[21,31].

Study limitations

The echocardiographically documented improvement of wall motion at follow-up was used as the definitive method for judging the accuracy of stress-induced functional improvement. We did not use an independent standard such as fluorodeoxyglucose or Thallium uptake.

About one half of the patients enrolled in this study did not undergo coronary revascularization and therefore did not enter the echocardiographic follow-up

programme. Some of these patients had no evidence of viable myocardium by either test; others had evidence of viable myocardium but no clinical indication for revascularization. Indeed, at present, the identification of viable myocardium is not in and of itself an indication for revascularization. As in any other patient with coronary artery disease, this decision should be based on clinical presentation, coronary anatomy, left ventricular function, and evidence of inducible ischaemia[3].

The main results of the study concerning the diagnosis of viability were based on 19 patients only, i.e. those who had an echocardiographic examination at follow-up. Therefore, the results should be considered preliminary, and need to be confirmed with larger series.

The study population involved a substantial number of individuals who had only mild left ventricular impairment, as the average ejection fraction was 41 ± 14%. After the present initial feasibility study, the infra-low dose test should be assessed in patients with severe left ventricular dysfunction, in whom the clinical question regarding the extent of viable tissue is more important[3]. This validation is currently ongoing, on a multicentre basis, with the VIDA (Viability Identification with Dipyridamole–Dobutamine Administration) project.

Infra-low dose dipyridamole: a haemodynamically neutral stress

Regional function can be modulated by extrinsic conditions such as systolic ventricular pressure, tethering by adjacent segments, preload changes, heart rate modifications[33]. At high (ischaemic) dipyridamole or dobutamine dosages, the effect on heart rate and blood pressure and the tethering effect from neighbouring segments and from the epicardial rim of muscle ('transmural tethering') make the increment of regional function more evident but less predictive of the real status of myocardium and of the subsequent functional recovery. Therefore, the ideal stress for viability should only minimally affect all these factors, since manipulation of haemodynamic variables can induce variations in wall motion and thickening independent of the local inotropic effect. Both low dose dobutamine and infra-low dose dipyridamole fulfil these requirements. Heart rate and systolic blood pressure were only minimally affected by dobutamine, were not affected at all by dipyridamole and neither stress induced ischaemia in any patient.

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